35 U.S.C.§ 112, First Paragraph, Rejection

The Examiner rejected claims 5, 21-22, and 24-26 under 35 U.S.C. § 112, first paragraph. This rejection, as it may be maintained with respect to the pending claims, is respectfully traversed.

Specifically, the Examiner alleges that the specification does not enable, or provide an adequate written description for, fragments of SEQ ID NO:2, e.g., fragments capable of binding a 4-1BB ligand. At page 16 of the specification, Applicant describes the preparation of a construct that encodes a portion of H4-1BB containing the signal peptide and the entire extracellular domain of H4-1BB. To ascertain which amino acid residues of H4-1BB are encoded by the construct, the sequence of the oligonucleotides used to amplify this coding region (see lines 17-22 of page 16) can be aligned with the cDNA sequence of H4-1BB shown in Figure 2. Such an analysis indicates that residues 1-186 of H4-1BB contain the signal sequence and the entire extracellular domain of H4-1BB. Thus, Applicant has provided the art worker with sufficient guidance from which the art worker can prepare other constructs which encode portions of the extracellular domain of H4-1BB. Moreover, peptide synthesis, rather than recombinant DNA methods, can be used to prepare an array of polypeptides that have different portions of SEQ ID NO:2. The Examiner is reminded that it is not necessary that a patent applicant make and test all the embodiments of his invention in order to meet the requirements of § 112. In re Angstadt, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976).

As for identifying whether a particular fragment of H4-1BB binds to a cell membrane ligand, it is Applicant's position that one of ordinary skill in the art in possession of the present specification and knowledge generally available to the art would be apprised of how to determine whether a particular fragment of SEQ ID NO:2 specifically binds to a cell membrane-bound molecule. Applicant's specification discloses that 4-1BB ligand is expressed on mature B cells and macrophage cell lines, but not on T cells (page 11). Thus, B cells, macrophage cell lines, and T cells can be used to screen fragments of SEQ ID NO:2 for their ability to specifically bind to B cells and/or macrophage and not to T cells. Alternatively, RNA is isolated from B cells or macrophage, and the isolated RNA used to prepare an expression library that can be screened with H4-1BB, or a portion thereof, to identify clones that express a H4-1BB ligand. Cells that

express recombinant H4-1BB ligand can then be employed to identify which regions of SEQ ID NO:2 specifically bind to the ligand.

Moreover, with respect to the "undue experimentation" alleged by the Examiner to screen constructs encoding specific regions of H4-1BB for their binding activity, the fact that the outcome of such a synthesis/screening program is unpredictable is precisely why a screening program is carried out. The Examiner simply cannot reasonably contend that a screening program to locate biomolecules with target biological or physical properties would not be carried out by the art because the results cannot be predicted in advance.

In fact, the Federal Circuit has explicitly recognized that the need, and methodologies required, to carry out extensive synthesis and screening programs to locate bioactive molecules do not constitute undue experimentation. In re Wands, 8 U.S.P.Q.2d 1400, 1406-1407 (Fed. Cir. 1988), the Court stated:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.

Likewise, practitioners in the art related to the present application would be well-equipped to prepare and screen portions of SEQ ID NO:2 to identify those which bind to ligands of H4-1BB. See also, Hybritech Inc. v. Monoclonal Antibodies Inc., 231 U.S.P.Q. 81, 84 (Fed. Cir. 1986) (evidence that screening methods used to identify characteristics [of monoclonal antibodies] were available to art convincing of enablement). Thus, the fact that a given claim may encompass a large number of polypeptides is not dispositive of the enablement issue, particularly in an art area in which the level of skill is very high and in which screening of large numbers of compounds has been standard practice for at least ten years (Ex parte Forman, 230 U.S.P.Q. 546 (Bd. App. 1986)).

Therefore, given Applicant's disclosure of the amino acid sequence of H4-1BB, i.e., SEQ ID NO:2, and the skill of the art worker in the relevant art area, it is Applicant's position that the preparation and screening of fragments of SEQ ID NO:2 to identify regions of SEQ ID NO:2 that bind to a cell membrane ligand is well within the skill of the art.

To the extent that the Examiner's rejection is based on the alleged failure of the application to meet the written description requirement for fragments of SEQ ID NO:2, the Examiner is requested to consider that application of the written description requirement is required (a) under 35 U.S.C. § 120, in determining whether a later-filed claim is entitled to the filing date of the parent application, (b) in interference practice, in determining whether a specification supports a count, and (c) where a claim of an original application is subsequently amended (In re Smith et al., 178 U.S.P.Q. 620, 623-24 (C.C.P.A. 1973)). While the Examiner has not articulated whether Applicant's alleged failure to meet the written description requirement is based on (a) or (c), it is Applicant's position that the claims, as amended, are clearly entitled to the filing date of the parent application, i.e., U.S. application Serial No. 08/122,796, to the above-identified application.

Moreover, it is well settled that Applicant need not literally describe every species in a genus to satisfy the written description requirement of § 112. Univ. of Calif. v. Eli Lilly and Co., 43 U.S.P.Q. at 1406 (C.A.F.C. 1997), citing to In re Angstadt, 537 F.2d at 502-02, 190 U.S.P.Q. at 218 (C.C.P.A. 1976); and In re Robins, 429 F.2d 452, 456-7, 166 U.S.P.Q. 552, 555 (C.C.P.A. 1970). What is required to describe a genus directed to a chemical material is "a precise definition, such as by structure, formula [or] chemical name". Fiers v. Revel, 984 F.2d 1164 at 1171, 25 U.S.P.Q.2d at 1601 (Fed. Cir. 1993). Such a structure or formula permits the art worker to visualize or recognize the identity of members of the claimed genus. Univ. of Calif. v. Eli Lilly and Co., 43 U.S.P.Q. at 1406 (C.A.F.C. 1997). Clearly, a claim that recites "SEQ ID NO:2 or a fragment thereof" is de facto a generic formula which permits the art worker to recognize species or "subunits" falling within the scope of that claim. Put another way, a claim to "a compound of formula X-Y-Z or a fragment thereof" is a full description of X-Y, Y-Z, X or Y. Therefore, it is respectfully urged that Applicant has adequately described SEQ ID NO:2 and fragments thereof and enabled its production.

With respect to the enablement of claim 26, the Examiner asserts that the specification provides (a) no dosage information, (b) no guidance as to how to make pharmaceutical formulations, (c) no reasonable expectation that the formulations would treat a disease or condition, e.g., suppress the immune system during organ transplantation, (d) which autoimmune diseases are to be treated, or (e) how to select enhancing versus suppressing activity.

Claim 26, as amended, is dependent on claim 24 and is directed to a pharmaceutical composition comprising a soluble H4-1BB polypeptide which comprises the extracellular domain of SEQ ID NO:2, or a fragment thereof, in admixture with a suitable diluent, carrier or excipient.

With respect to (c)-(e), the specification discloses and illustrates that 4-1BB can be used to suppress T cell-dependent immune responses. See pages 17-18 and Figures 5(a)-(c). Since 4-1BB production is induced during T cell activation, blocking the interaction of T cells with antigen presenting cells which express H4-1BB ligand by contacting cells with a polypeptide such as that recited in claim 24 will lead to immunosuppression.

Moreover, one of ordinary skill in the art is capable of determining whether a disease is associated with a specific immune cell, e.g., a B cell or a T cell, and whether that disease is associated with aberrant stimulation or suppression of a particular immune cell (see, for example, U.S. Patent No. 5,645,820 which discloses autoimmune diseases associated with B cells and autoimmune diseases associated with T cells). Thus, if the proliferation of T cells in a particular disease or pathology is excessive, the suppression of those T cells would be indicated. Moreover, it is within the skill of the practitioner to use *in vitro* assays, or an animal model, to test an agent for its ability to stimulate or suppress an immune response.

The Examiner is also requested to note that the reaction of T cell receptors, such as isotypes of the leukocyte common antigen, with blocking or "anergizing" ligands such as anti-CD45R monoclonal antibodies has been shown to be effective in animals models to reverse transplant rejection. See, for example, WO 96/32965 ("CD45RB Binding Compounds for the Prevention of Transplant Rejection"; Zheng et al., Transplant. Proc., 27, 389 (1995); and Lazarovits, Transplantation, 54, 724 (1992).

With respect to (a) and (b), it is Applicant's position that the selection of dosages and the preparation of pharmaceutical formulations is well within the skill of the art, and is necessarily empirical and patient-dependent. (See, In re Johnson, 282 F.2d 370, 127 U.S.P.Q. 216 (C.C.P.A. 1960) (the selection of suitable dosages is within the skill of the art)). Methods for extrapolating from dosages effective in animals to dosages effective in humans are known to the art. See, for example, U.S. Patent No. 5,294,430. Applicant need not teach, and preferably omits, that which

is known to the art. Hybritech Inc. v. Monoclonal Antibodies Inc., 231 U.S.P.Q. 81, 84 (Fed. Cir. 1986).

With respect to pharmaceutical formulations, the specification notes that lymphokines, e.g., interferons, interleukins, erythropoietin, and tumor necrosis factor, have been produced for therapeutic use (page 2). Moreover, the Examiner has acknowledged that "[p]harmaceutical compositions consisting of secreted forms of lymphocytic proteins are common to the art" (at page 8 of the Office Action dated April 19, 1996). Further, soluble murine 4-1BB was administered to a rat to prepare monoclonal antibodies specific for 4-1BB (Pollock et al., J. Immunol., 150, 771 (1993)), copy attached hereto). Thus, it is well within the skill of the art worker, in possession of Applicant's specification and knowledge available to the art, to prepare pharmaceutical compositions comprising H4-1BB or a portion thereof and select appropriate dosages.

It is respectfully submitted that the pending claims are in conformance with the requirements of 35 U.S.C. § 112, first paragraph. Hence, the Examiner is requested to withdraw the § 112(1) rejection of the claims.

The 35 U.S.C.§ 103 Rejection

The Examiner rejected claims 5-6, 21-22 and 24 under 35 U.S.C. § 103(a) as being unpatentable over Schwarz et al. (GenBank Accession No: L12964) in view of page 45 of Ayala et al. (Mod. Genetics, Benjamin Cummings Publ. (1980)). As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

Schwarz et al. disclose the nucleotide sequence encoding, and the inferred amino acid sequence of, ILA. The inferred amino acid sequence of ILA has one amino acid substitution relative to Applicant's SEQ ID NO:2.

The Examiner is respectfully requested to consider the Rule 131 Declaration enclosed herewith. In the Rule 131 Declaration, Applicant declares and documents that in the United States, he had conceived of isolating and purifying DNA encoding human 4-1BB prior to the April 22, 1993 publication date of Schwarz et al. Moreover, in the Declaration, Applicant declares and documents that, after conception, he proceeded diligently to reduce the invention to practice in the United States.

Since Applicant need demonstrate only so much of the claimed invention as taught by the prior art reference, it is respectfully submitted that Schwarz et al. is not available as prior art against the present claims. In re Stempel, 113 U.S. P.Q. 77 (C.C.P.A. 1957). Therefore, Schwarz et al. cannot be used to support a rejection of these claims under 35 U.S.C. § 103(a). Therefore, the enclosed Rule 131 Declaration properly establishes Applicant's date of invention as earlier than the effective date of Schwarz et al.

Page 45 of Ayala et al. discloses that many, and possibly all, genes have multiple alleles. Nevertheless, there is nothing at page 45 of this reference that teaches or suggests the preparation or isolation of a polypeptide having SEQ ID NO:2 or a fragment thereof. Thus, this reference does not render Applicant's invention obvious.

Based on the discussion above, the Examiner is respectfully requested to withdraw the § 103(a) rejection of the claims.

CONCLUSION

Applicant believes the claims are in condition for allowance and request reconsideration of the application and allowance of the claims. The Examiner is invited to telephone the below-signed attorney at (612) 373-6959 to discuss any questions which may remain with respect to the present application.

Respectfully submitted,

By their Representatives,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Box AF, Assistant Commissioner of Patents, Washington, D.C. 20231 on **October 26, 1998.**

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